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JOHN FITCH LANDON, M.D., Editor

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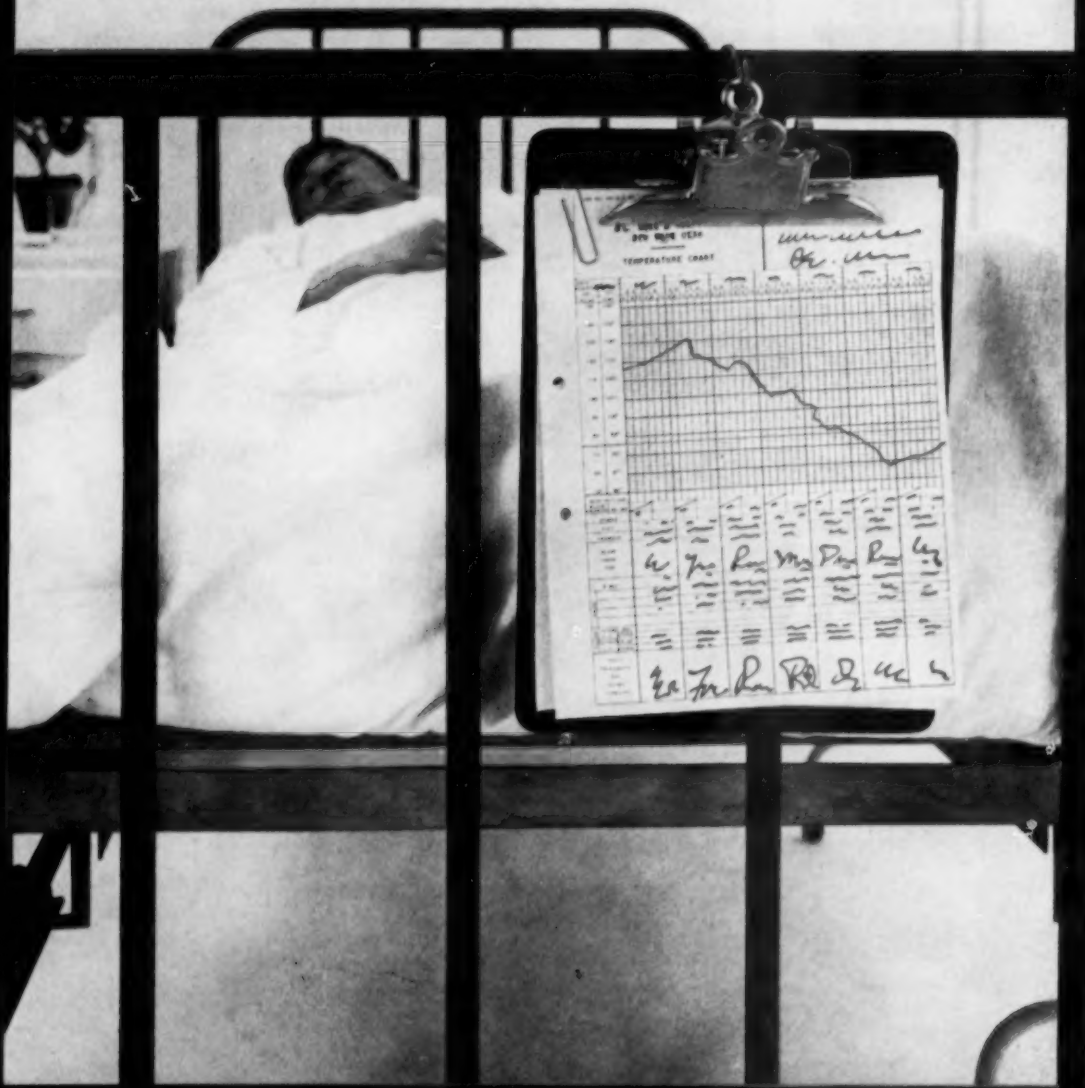

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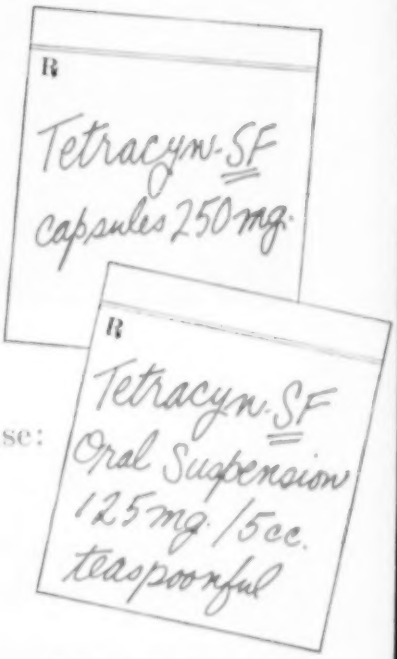

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ARCHIVES OF PEDIATRICS

VOL. 72 JULY 1955 No. 7

JOHN FITCH LANDON, M.D., Editor

TUBERCULOUS MENINGITIS*
A REVIEW

HERBERT M. KRAVITZ, M.D.
New York.

History. Tuberculous meningitis was first recognized as a disease entity in the early 19th century[5]. At that time, a French physician, named Bayle, successfully correlated pulmonary tuberculosis with tuberculosis in other organs, including the recognition of tuberculous meningitis. Gerhard, an American physician, who first differentiated typhoid from typhus in 1833, is credited with having done the first accurate clinical study of tuberculous meningitis in children. However, when one correlates the finding of tuberculous lesions of the vertebrae in 3,000-year-old Egyptian mummies with current knowledge of the pathogenesis of tuberculous meningitis, it appears probable that this disease was present during the early beginnings of civilization.

CASE REPORT

A six-year-old Puerto Rican girl, R.N., was admitted to the Pediatric Service of Metropolitan Hospital, New York City, on July 6, 1954 complaining of abdominal pain, occasional fever, poor appetite and weight loss; all of approximately two weeks' duration, as well as severe vomiting of about five days' duration.

The child had been well until 16 days before admission when she developed a fever and started vomiting. During this time, the mother noted that her daughter's temperature rose and fell to peaks

*From New York Medical College-Metropolitan Hospital, New York.

of 103°-104° F. The vomiting was sporadic and not projectile. The abdominal pain was localized to the umbilical area and was of a transient nature. There were no changes in bowel habits or bloody stools during this time.

Shortly after the onset of symptoms, the mother had taken the child to a clinic where it received, on separate occasions, two doses of penicillin for what was diagnosed as an acute upper respiratory infection. However, when the child failed to respond, she was referred for hospitalization.

The past history was not especially revealing. The child had been vaccinated several years ago, but had not received any other immunization. All accidents and operations were denied. Previous illnesses, including measles and a worm infection had been treated in Puerto Rico two years ago. However, two months ago the child reported passing an eight-inch worm in the stool for which she received no treatment. The mother also claimed that her daughter has had "asthma" since birth, although there have not been any acute episodes since the child entered the United States one year ago. Growth and development appear to have progressed satisfactorily.

The mother denied any family history of tuberculosis, diabetes, or "bad blood." The patient has one older sister (age 7) who is alive and well.

Physical examination on admission showed a pale, lethargic, malnourished, irritable white child not in any acute distress. Temperature 101° F.; pulse 80; blood pressure 100/75. There was questionable neck rigidity, sluggish bicep reflexes, and hypersensitivity of the skin of the lower extremities. All other pathological reflexes were negative, though a positive Kernig's was elicited three days later. The pupils responded sluggishly to light. The left optic disc had an indistinct margin, although there was no papilledema. The right disc was normal. The tonsils were mildly injected and there was slight cervical lymph-adenopathy. The chest was clear to percussion and auscultation and the abdomen was negative.

A provisional diagnosis of meningitis, etiology to be determined, and an incidental parasitic infection was made. An emergency diagnostic spinal tap was performed. This showed a pleocytosis of 350 cells (mostly lymphs), increased protein of 73 mg. per cent,

decreased sugar of 18 mg. per cent and chlorides of 600 mg. per cent. The blood count on admission was inaccurate, due to a laboratory error. However, it was repeated on the following day and showed RBC 4.3 million, WBC 14,300 with 73 per cent polys and a sedimentation rate of 10/74. In light of the spinal fluid findings, the diagnosis of tuberculous meningitis was made and therapy with I.M. streptomycin 1.6 gm./day, para-amino salicylic acid 0.1 gm./lb./day, and isoniazid 4 mg./lb./day was begun. (One week later, dihydrostreptomycin 1 gm./day was substituted for the streptomycin. On the third week of hospitalization, the dihydrostreptomycin was cut to one gram twice weekly, and this dose is presently being given along with PAS and isoniazid in the doses mentioned above.)

Subsequently, blood cultures for predominating organisms and spinal fluid culture for bacteria and tuberculosis were done. The blood cultures and spinal fluid showed no bacteria, though the results of the cultures for tuberculosis were also negative. A chest x-ray on admission showed increased hilar markings compatible with the diagnosis of pulmonary tuberculosis. A Mantoux was found to be positive in 1:10,000 dilution.

SPINAL FLUID FINDINGS

Date	7-6-54	7-7-54	7-22-54	8-4-54	8-26-54
Cells	352	440	150	20	75
Protein	73	113	...	112	78 mg%
Sugar	18	28	58	53	56 mg%
Chlorides	600	625	675	705	720 mg%

The hospital course was one of progressive improvement. The temperature was septic in nature with spikes of 102° F. during the first four weeks, although it has remained normal since then. Spinal fluid findings (see chart) have shown a gradual decrease in cells, a rise in sugar to normal levels, and a rise in chlorides to normal levels though proteins have remained elevated. A chest x-ray, taken one month after admission, showed a considerable increase in pulmonary markings which were probably due to tuberculous mediastinal nodes. The remaining lung fields were normal. The urine was negative and, several weeks after admission, a positive stool for Ascaris ova was reported.

In an attempt to locate tuberculous contacts, an invesigation of the child's home was made. This revealed that the family of

four lived in a one-room apartment in a slum area. The mother and older sister were well and had negative chest x-rays. However, the father, who was unemployed, refused to submit to a physical or x-ray examination.

Clinically, the child regained her appetite about a week after admission. Her weight increased from 38 to 45 pounds and all physical signs have disappeared. However, the child continued to be irritable and somewhat lethargic until recently.

A current physical examination revealed no abnormal findings. The chest was clear to percussion and auscultation, the eye grounds appeared normal, and there were no pathological reflexes. The child is moderately active, eating well, and fully aware of her surroundings, though she is still somewhat irritable when approached by "a white uniform."

Incidence. Tuberculous meningitis has its peak incidence during the first three years of life, though it is said to be rare in infants under six months of age.[1] It is almost always secondary to tuberculous diseases elsewhere in the body, with a primary focus usually in the lung. However, this primary focus may be so minute as to escape detection by x-ray and may only be noted on microscopic examination at post-mortem. The actual incidence of meningitis resulting from primary foci elsewhere in the body is unknown.[25]

Pathogenesis. The pathogenesis of tuberculous meningitis is disputed. According to Anderson,[6] there are three main theories: (1) direct hematogenous infection of the cerebral spinal fluid; (2) hematogenous infection of the choroid plexus with the development of tubercles which later infect the meninges; and (3) spread to the superficial cortex via the blood stream with the development of tubercles which later rupture or spread infection to the meninges. However, most authorities accept the findings of Rich and McCordock[8] which indicate that tuberculous meningitis is the result of secondary involvement of the meninges caused by the discharge of tuberculous material from older foci in the brain, spinal cord, choroid plexus, or, rarely, vertebrae.

At autopsy, the brain is swollen and edematous. A greenish exudate may be seen in the subarachnoid space as well as at the base of the brain. Minute, opaque, yellowish tubercles are usually seen about the subarachnoid and choroidal blood vessels. The vessel walls may become necrotic and thrombosed, giving rise to

local infarctions. The meninges are thickened, due to fibroblastic reactions. The inflammatory process often involves the cortical tissue so that tuberculous meningitis is actually a meningoencephalitis.

Symptomatology. The clinical symptomatology is not specific with the earliest findings being that of a mild encephalitis. The onset is gradual, though it may be abrupt. Failure of the child to play, irritability, sleepiness, and digestive disturbances, i.e., vomiting, constipation, anorexia, with slight elevation of temperature are frequently the earliest indications of the disease. Meningeal signs are usually next to appear. These may consist of vomiting, photophobia, hyperesthesia, nystagmus, nuchal rigidity, flushing of the skin due to vasomotor spasm (tache cerebrale), convulsions, spasms, abnormal reflexes, such as Brudzinski and Kernig's signs, and elevated temperatures.

The blood picture is not striking. Early in the course of the disease the white count is usually within the upper or lower limits of normal. However, with progression, there is a moderate to high leukocytosis with a predominance of neutrophiles.

In untreated cases, the disease is progressive with death commonly occurring from two to three weeks after the onset of the initial symptoms. The meningeal signs are replaced by paralysis, temperatures of 106°-107° F. and coma followed by death. Temporary remissions with improvement may prolong the course for many weeks.

Diagnosis. There is only one absolute way of making a positive diagnosis of tuberculous meningitis and that is by demonstration of tubercule bacilli in the spinal fluid by smears or culture. A presumptive diagnosis may be based on clinical symptomatology, history of exposure to a tuberculous contact, typical spinal fluid findings, a positive tuberculin skin test, and the demonstration of a primary focus elsewhere in the body.

Typical spinal fluid findings consist of increased pressure, a pleocytosis of 50-500 cells (Holt[1] has reported cell counts of 16 to 3000 per cu. ml.), elevated total protein, usually above 100 mg./100 ml., decreased glucose, commonly below 36 mg. per 100 ml., and chlorides usually reduced below 700 mg. per 100 ml. Very early in the disease, neutrophiles predominate in the spinal fluid, though lymphocytes are most commonly found by the time the

child is brought into the hospital. The tuberculin test is usually positive early in the disease. However, tuberculin allergy is commonly lost during the terminal stages.

Serous Tuberculous Meningitis. Lincoln[9] has described a tuberculous serous meningitis which results from irritation of the meninges by a tuberculoma without discharge of organisms into the subarachnoid space. Clinically, the symptoms of serous meningitis are usually milder and the prognosis better. Differentiation from classical forms of tuberculous meningitis is based on spinal fluid findings. In serous forms, there is increased pressure and cells, though chemical findings remain normal. A few acid-fast bacilli may be recovered, though they are not usual. Since some of Lincoln's patients subsequently went on to develop classical meningitis, and in view of the accepted pathogenesis of tuberculous meningitis, it appears that serous meningitis is probably an arrested prodromal stage of classical meningitis.

Therapy. Using current methods of therapy, various investigators[12] have reported arrest or recovery from tuberculous meningitis in 25 to 75 per cent of their cases. The prognosis in these cases has been shown to be influenced by age, the extent and severity of symptoms, and the therapeutic measures used.[17, 19] Despite combined drug therapy, infants under one year of age have the worst prognosis, children age 1 to 6 years have a better prognosis, and those in the 6 to 20 year old group have the best chance of recovery.[19] The more severe the symptoms, the graver the prognosis. In one series[17] of five year follow-ups after drug therapy, it was noted that the mortality rate was not increased in children who were found to have meningitis associated with miliary tuberculosis. However, if while being treated with streptomycin, the child developed meningitis, the chances of recovery were decreased. The values of the spinal fluid constituents at the time treatment was begun were not significant in regard to altering the prognosis.

Recently, Waddell et al. have confirmed that patients who had meningitis with associated miliary or pulmonary tuberculosis did not have a poorer prognosis than those without demonstrable pulmonary complications.[26]

In another series of cases, the failure in recovering tubercle bacilli from the spinal fluid had little prognostic value. It was found that the virulence of the meningitis can be equally severe

whether or not the spinal fluid culture is positive.[18]

The sedimentation rate (ESR) has also been shown to be of no value in estimating the course or prognosis of this disease in children.[22]

Before the advent of antituberculous drugs, tuberculous meningitis was almost 100 per cent fatal. With the introduction of new chemotherapeutic agents, the prognosis became better and better. Accurate mortality and morbidity figures are not available at this time due to the recent introduction of new drugs, which have not been fully evaluated, clinically. Before attempting to present the results of some of the more recent investigations, a short summary of the available antituberculous agents and their significant pharmacology will be given.

Streptomycin was first isolated in 1944 from the fungus, Streptomyces griseus. The drug was found to be effective against tubercle bacilli and is believed to act by interfering with normal cell division. It is bacteriostatic in low doses, and bacteriocidal in high doses, with increased killing rate as concentration increases.[4] (The Streptomycin type drugs are unique in this last respect.) However, in prolonged use, the drug is neurotoxic and produces 8th nerve damage. Streptomycin is not absorbed orally and must be given intramuscularly. In individuals without meningitis, the drug does not penetrate the hemocephalic barrier. However, with meningeal infection, about one-fifth of the serum concentration will be found in the cerebral spinal fluid.[4]

Dihydrostreptomycin is similar in properties to streptomycin except that the dihydro-compound produces less vestibular damage. However, recent studies in Denmark[16] suggest that dihydrostreptomycin be discarded in favor of streptomycin. While prolonged use of streptomycin will produce vestibular damage, prolonged use of the dihydro-compound will produce loss of hearing with impaired vestibular function. Hence, it is felt that loss of vestibular with retained auditory function is better tolerated than loss of both hearing and balance as occurs with dihydrostreptomycin. The dihydro-preparation should never be given intrathecally.[4] Nelson has reported that a combination of 50 per cent streptomycin with 50 per cent dihydrostreptomycin has been shown to have less toxicity in adults than either drug alone.[3] The value of this combination in children is still under investigation.

Para Aminosalicylic Acid (PAS) was synthesized in 1943. PAS is bacteriostatic, but unlike streptomycin, it is not bacteriocidal and does not change the staining properties of the bacillus.[6] When given orally, the drug is rapidly absorbed and excreted. This necessitates frequent high dosages in order to maintain blood level. In general, PAS is less effective therapeutically than streptomycin, though the latter drug is more toxic.

Promizole,[8] a sulfone, was synthesized in 1945. It is tuberculostatic and may be given orally. Promizole is toxic and may produce reversible hemolytic anemias as well as act as a goiterogenic agent. Its effectiveness in meningitis is questionable and in a Public Health Service survey last year it was concluded that the drug was of no value as an adjuvant to combined streptomycin-PAS therapy.[24]

Thiosemicarbazones[4] (Tibione) besides being toxic, has been shown to be ineffective in tuberculous meningitis. *Viomycin,*[7] recently isolated from Streptomyces puniceus, also has antituberculous activity similar to streptomycin. However, this drug is much more toxic than streptomycin and, hence, can only be used for a very short period in selected cases.

Isoniazid is one of the newest and most promising of the antituberculous drugs. It was first found to be clinically effective during the later months of 1951. Radioactive isotope studies[23] have shown this drug to have a delayed bacteriostatic effect on the growth of susceptible tuberculous organisms. Streptomycin has an immediate effect.) Massive quantities of isoniazid were no more effective in vitro than small quantities. This drug may be given orally. It readily enters the spinal fluid and is relatively nontoxic. Doses of up to 40 mg./kg./day have been used in children without significant toxic effects.[21] Reactions contraindicating further use of this drug are rare but include psychosis, convulsions, peripheral neuropathy, severe allergy and difficulty in micturation.[11]

Of the three major drugs (streptomycin, isoniazid and PAS) used today in the treatment of tuberculous meningitis, none should be used alone because of the rapid development of drug resistant strains. However, when used in combination, the development of resistant strains is inhibited to a great extent.[1, 2, 4, 10, 11]

The value of giving streptomycin intrathecally has been disputed. Several investigators claim that intrathecal streptomycin only in-

creases the possibilities of developing spinal blocks and other complications.[22, 27] Some groups feel that isoniazid eliminated the need for intrathecal medication,[1, 26] or that sufficient streptomycin enters the spinal fluid in meningitis.[4] However, other men still feel that intrathecal streptomycin is indicated, at least, until further studies are available.[2, 14] In view of the fact that there appears to be a lag between the time isoniazid is given and the time that it takes effect (in vitro studies) which does not appear to occur with streptomycin, it might be advisable to administer streptomycin intrathecally for the first week of treatment (along with combined extrathecal drug therapy). Further clinical studies would be needed to evaluate this hypothesis.

One of the common complications of tuberculous meningitis is the development of obstruction to the flow of the cerebral spinal fluid. In an effort to prevent this, Shane and Riley have combined antituberculous drugs with cortisone in order to limit exudate formation. They feel that cortisone can be safely used in the presence of active tuberculosis *provided* adequate chemotherapy is sustained. In two fatal cases treated with cortisone, they have demonstrated reduced exudate formation.[20]

A German group has found that some cases of hydrocephalus, associated with spinal block in tuberculous meningitis, will respond to persistant antimicrobial therapy. They advise that surgical procedures for the relief of the hydrocephalus should be postponed in favor of prolonged chemotherapy.[19]

The optimal length of any course of treatment has not been determined conclusively. Isoniazid has not been available for general use long enough to permit long term follow-up studies. However, one English group[23] advocated continuing treatment until the CSF sugar rises above 50mg./100ml. They claim that one should not expect cell counts and protein levels to fall to normal until many months after treatment has ceased. Lincoln feels that treatment should be continued until CSF values are normal.[13] Nelson[3] advocates the use of daily streptomycin intrathecally for 40 to 60 days until the spinal fluid has less than 30 cells/cu. mm., protein below 100 mg./100 ml. and an average normal sugar value. He combines this therapy with equal quantities of strepto and dihydrostreptomycin I.M. (q. 12 h.) for six months or more. PAS is given concurrently with the streptomycin and is continued for one year

after the streptomycin is stopped. As an alternate routine, he suggests substituting isoniazid for the PAS that is given concurrently with the streptomycin. However, when the streptomycin is discontinued, he advises substituting PAS for the isoniazid and continuing the PAS for one year.

Holt suggests the use of streptomycin daily until clinical improvement is noted and then giving one gram twice weekly for one year. Isoniazid and promizole are used concurrently.[1]

Waddell et al. advise using streptomycin daily until the CSF findings are normal and then continuing the same dose twice weekly for a total course of at least six months. They also give PAS and isoniazid concurrently in divided daily doses for at least twelve months. At the present time, they do not use any intrathecal therapy.[26]

In general, the dosages advised most commonly in the literature for the various antituberculous drugs are:

(1) Streptomycin: Intrathecal; 25 to 100 mg./day. Intramuscular; 40 mg./lb./day (not to exceed one gram daily).[2, 21]

(2) Combined streptomycin and dihydrostreptomycin (50 per cent of each drug). Intramuscular: Same dose as given for streptomycin alone (40 mg./lb./day).[2]

(3) Isoniazid: 4.5 mg./lb./day in divided oral doses.[1, 2, 21]

(4) PAS: 0.1 to 0.23 gm./lb./day in divided oral doses.[2, 3, 21]

(5) Promizole: 0.5 to 3 gm. per day (total) in divided oral doses as tolerated.[1, 3, 4]

Bed rest, "play therapy," and good nutrition are also vital points in the treatment of any type of tuberculosis and should not be overlooked. Hospitalization for at least one year is usually required.[12]

CONCLUSION

New antituberculous drugs have given promise in the treatment of tuberculous meningitis. A once universally fatal disease, tuberculous meningitis can now be arrested in 25 to 75 per cent of cases, though long term follow-up studies are not yet available.

Among some of the problems that still remain to be clarified are the optimal length of therapy required, the incidence of recurrences, the possibility of widespread drug fastness developing, the most effective combinations of chemotherapeutic agents to use, and the value of intrathecal and prophylactic therapy.

The tubercle bacillus has survived to infect mankind for over 3,000 years. The battle to control tuberculosis looks promising at this time, but many years of research still must be undertaken before any valid account can be written as to the effectiveness of recent therapeutic advances.

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RETROLENTAL FIBROPLASIA

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History. A new disease has emerged which had its birth scarcely over ten years ago. For the past ten years retrolental fibroplasia has represented a new problem, both clinically and epidemiologically. Today retrolental fibroplasia is the commonest late complication of prematurity. Fifteen years ago blindness from this cause was so rare that the disease was not recognized. The first description of the disease was made by Terry in 1942, and it was Terry who later named the disease. In the following six years there was some question as to whether retrolental fibroplasia was a distinct disease, and uncertainty about differentiating this disease from other retinopathies. In 1948, Owens and Owens established that retrolental fibroplasia developed in premature infants, who had normal eyes at birth.

Incidence. Retrolental fibroplasia is not a reportable disease, except in New York State, hence its incidence is little known; however, there is no question that an absolute increase in its incidence has occurred. In a survey undertaken by the National Society for the Prevention of Blindness it was found that two-thirds of all the new cases of preschool blindness, occurring in 1950, were due to this condition. This represents a 50 per cent increase over the figures in 1943. Although there has been a marked decrease of blindness from all other causes, viz., infection, trauma, etc., the rate of blindness due to retrolental fibroplasia has risen steeply since 1943. This significant rise cannot be explained completely by the assumption that the disease was formerly undiagnosed, or, that more prematures now live long enough to acquire the disease. The National Society for the Prevention of Blindness presented statistics to partially verify this. From a study of 2796 cases of blindness in persons under twenty-one years of age in seven states, it was estimated that the average annual incidence of blindness per 100,000 population was around 1.5 per cent for many years before 1935. Thereafter, with improved control primarily of ocular infections, the rate dropped until 1941-1945. Since 1941-1945 not only has the relative incidence of retrolental fibroplasia increased significantly, but its increase has been so great as to cause the

average annual incidence of blindness per 100,000 population in the years 1946-1950 to exceed the level prior to 1935. In the years 1946-1950, retrolental fibroplasia accounted for one-third of all blindness in persons under 21 years of age.

Distribution and Age at Onset. Retrolental fibroplasia is generally restricted to infants whose birth weights are 3 ± 0.5 pounds (1300 ± 200 gms.), and is extremely rare in infants weighing 2,000 gms. or more, although several cases have been reported in full term infants. It is generally accepted that the greater the degree of prematurity the greater the incidence of retrolental fibroplasia. Sex distribution is approximately equal. Maternal factors or complications, other than those which cause premature birth, have no demonstrable effect. The age of onset is stated to be from 3 weeks to 6 months with most cases becoming manifest by the end of the third month. It has been observed that the shorter the period of gestation the later was the onset of the disease and *vice versa* to the point where intrauterine development has proceeded beyond the critical phase of ocular growth when it can no longer be influenced by an adverse extrauterine environment. The onset of the disease, and the critical or susceptible phase of development, may be related to weight rather than to length of gestation or age after birth. If this is done, it is found that the typical weight at onset is 1800-2200 gms. The vulnerable stage appears to be around the eighth month of conceptual age—a time when the fundus is being rapidly vascularized. Before seven months of conceptual age, early signs of retrolental fibroplasia have not been described.

Pathology. Retrolental fibroplasia is a process of angioblastic outgrowth into the vitreous of capillary vessels derived from the developing retina. In its early phases the process is reversible, but its ultimate expression, if it progresses, is a variable mass of contracting scar tissue in the vitreous with varying degrees of retinal detachment causing partial or complete blindness.

The National Society for the Prevention of Blindness divides the pathological process into an active phase and a cicatricial phase. The active phase is further divided into five structural stages or categories of increasing severity. The cicatricial phase is divide into five less clearly defined grades of severity.

Active Phase.

Stage I. Dilatation and tortuosity of the retinal vessels, hemorrhages may or may not be present, early neovascularization may be present in the extreme periphery of the visible fundus.

Stage II. Stage I, plus neovascularization and some peripheral retinal clouding, hemorrhages are usually present; vitreous clouding may or may not be present; spontaneous regression may occur.

Stage III. Stage II, plus retinal detachment in the periphery of the fundus; spontaneous regression is unlikely.

Stage IV. Hemispheric or circumferential retinal detachment with elevation of the retina over a large area, but with some retina still in position.

Stage V. Complete retinal detachment.

Cicatricial Phase.

Grade I. A small mass of opaque tissue in the periphery of the fundus with no visible retinal detachment.

Grade II. A larger mass of opaque tissue in the periphery of the fundus with some localized retinal detachment. Cases ending in Grade I or Grade II have useful vision.

Grade III. Larger masses of opaque tissue in the periphery incorporating retinal folds and larger areas of retinal detachment.

Grade IV. Retrolental tissue covers a part of the pupillary area, a red reflex only over a sector of the fundus may be seen.

Grade V. Retrolental tissue covering the entire pupillary area, no fundus reflex present.

Ingalls advanced a simplified nomenclature and maintains that two categories are sufficient—one to designate the early and reversible manifestations, and the other for the late and irreversible changes in the fundi. He proposes that Stages I and II signs be grouped together—tortuosity, engorgement, hemorrhage of retinal vessels and patchy edema of the retina. These manifestations may develop or regress rapidly and may escape detection. Stages IV and V include growth of neovascular tissue into the vitreous and formation of a grayish membrane in the retrolental space. These changes develop many weeks and months after the earlier manifestations. The border line of this practical two-category classification is Stage III of the five-category classification.

Etiology and Precipitating Factors: Oxygen. The influence of high oxygen concentrations with the resultant excessive levels of tissue oxygen saturation has received much study, and its role

in the genesis of retrolental fibroplasia is now established. The evolution of medical opinion concerning the state of oxygenation as related to retrolental fibroplasia is interesting and rather typical.

The first hypothesis was that fetal anoxia was responsible. This received support by the data forwarded by Ingalls, Terry, Krause, Reese and Payne—data indicating a high rate of placental disease, multiple births, toxemia and hemorrhage among the mothers of infants in whom retrolental fibroplasia developed. In May 1951, Lelong suggested that hyperoxia rather than anoxia was the prime factor. This view was given support by the findings of Campbell that retrolental fibroplasia developed in 23 of 123 premature infants maintained at 40 to 60 per cent oxygen and only in 4 of 58 prematurely born infants given little or no supplemental oxygen. Szewczyk later provided evidence for reconciling both the anoxic and hyperoxic theories. He found that infants with the early stages of retrolental fibroplasia improved when placed in an atmosphere of 60 to 70 per cent oxygen whereas early signs of retrolental fibroplasia were induced when infants, previously maintained in atmospheres of high oxygen concentration, were abruptly exposed to room air. Szewczyk interpreted the latter changes as being due to the inability of the infant to make the required physiologic changes of acclimatization before rapidly differentiating areas, such as the retina, have been harmed.

It is not yet settled whether the etiologic mechanism is a simple toxic effect of hyperoxia or a more complex one involving physicochemical changes upon the sudden change from one atmosphere to another producing ultimate hyperoxia.

Electrolytes. At the Chicago Lying-in Hospital an interesting study has been conducted relating the serum sodium levels to the incidence of retrolental fibroplasia. It was found that the incidence of blindness due to retrolental fibroplasia was 7 in 103 infants born weighing less than 1500 gms. where cow's milk formula contained 20 MEq. or less of sodium per liter and 21 in 48 where cow's milk formula contained 56 MEq. per liter. In the three years following this study, the sodium content of premature infants' formulae was held at the lower level and the incidence of blindness, due to retrolental fibroplasia in infants born weighing less than 1500 gms., has been less than 3 per cent.

The results of the above study were confirmed by the Univer-

sity of Texas School of Medicine. They found that 4 of 12 premature infants devoleped retrolental fibroplasia when they were maintained on a formula containing 23 MEq. per liter and 15 of 17 developed retrolental fibroplasia when their formulae contained 56 MEq. per liter.

Blood Transfusions. Vitreous and retinal hemorrhages after blood transfusions to premature infants with retrolental fibroplasia is common and renders the prognosis poor.

RECOMMENDATIONS

1. Oxygen is probably over-used both in concentration and duration. It should be used more discriminately and only where there is a definite indication, viz., cyanosis or respiratory difficulty. It probably should be administered in no greater concentrations than the minimum required to keep an infant pink.

2. In view of the findings of the Chicago Lying-in Hospital and the University of Texas, that excessive sodium levels may be a factor, the intake of sodium (Na) should be kept at low levels. Sodium chloride should not be added to the formula, and in the management of disease in premature infants, when parenteral fluids are indicated, whenever possible dextrose and water should be used rather than saline.

3. Blood transfusions to premature infants should be given only when absolutely necessary, and the amount given should not exceed 5 cc. per pound. The presence of retrolental fibroplasia is a relative contra-indication for blood transfusions in terms of prognosis for vision.

4. Once the disease has progressed beyond the reversible stage, there is no treatment known, but mydriatics should be administered to keep the iris mobile, and to prevent the development of posterior synecchiae which may lead to secondary glaucoma, a not uncommon complication.

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METHODS BY WHICH THE NEONATAL DEATH RATE MAY BE REDUCED

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The neonatal death rate was reduced at Hillcrest Medical Center, Tulsa, Oklahoma, from 22.1 per thousand in 1953 to 13.6 per thousand in 1954 (32 deaths in 2,364 live births). This is one of the lowest death rates in the nation.

In 1953 there were 2,138 deliveries with 47 neonatal deaths. The number of prematures was 71 with 34 deaths. Total live births 2,115; total still births 23 with a rate per thousand of 11. Total perinatal mortality was 32 per thousand in 1953 as contrasted with 25.5 per thousand in 1954. The causes of neonatal death in 1953 were as follows:

Class A—Congenital anomalies incompatible with life, 5.
Class B—Weight under 400 grams, 1.
Class C—Immature under 1000 grams, only 10 per cent salvage expected, 13.
Class D—Weight 1,000 to 1,500 grams 50 per cent salvage expected, 12; weight 1,500 to 2,500 grams, 80 per cent salvage expected, 8 cases.
Class E—Erythroblastosis, 2.
Class F—Cerebral hemorrhage, 5.
Class G—Diabetes of mother, 1.
Class H—Hyaline membrane, 2.
Class I—Atelectasis, 9.
Class J—Pneumonia, 2 Friedlander's and 1 A. Aerogenes.

The chart of each of these infants was analyzed, as to the weight; how soon fed and how often, whether by gavage or nipple, whether placed in airlock, whether given vitamin K or an antibiotic, whether given a stimulant, whether given subcutaneous fluids, when the acute distress developed; whether an x-ray was taken, how the child was delivered, and how long the child lived.

It was decided that the outlined procedure should be followed: Feeding by eye dropper should be discontinued; feeding too soon should not be done. As 23 of these children had been placed in the airlock, probably without adequate suctioning, it was decided

to suction the stomachs of all premature, breech, and difficult deliveries as well as cesarean sections, and to place them in O_2 with alevaire, in preference to the airlock. It was decided not to give subcutaneous fluids within the first 48 hours, as a child is edematous at birth; to give vitamin K, 75 mgm. to the mother of the expected premature infant at the onset of labor; to give vitamin K, mgm. to all prematures and infants with prolonged second stage over one hour, in difficult forceps and breech deliveries; to take early x-ray of any infant who remained cyanotic over 4 hours, or had respiratory difficulty, even if no fever; to give early antibiotics if respiratory difficulty continued more than one day.

If penicillin is not effective in 12 to 24 hours, chloromycetin is the drug of choice, as it is has the widest range, and is the only drug which would have prevented the deaths of the three pneumonia cases who had Friedlander's and aerogenes. Cord-Coombs test on all RH negative mothers should be made; if positive Coombs is found, to give an exchange transfusion within eight hours.

In order to show the improvement that was made in the neonatal rates following institution of these procedures, we will report the 1954 neonatal rate, the first half of the year as compared with the second half. From January to July 1954, there were 20 deaths per 1,000 deliveries. Causes of death were: Immaturity, weight under 1,000 gm., 2; weight under 1,500 gm., 1; weight under 2,500 gm., 10; congenital heart disease, 3; erythroblastosis, 1; Atelectasis, 1; high forceps, 1; overloaded circulation with transfusion, 1.

From July through December 1954 there were 12 deaths in over 1,200 deliveries or a rate of 10 per thousand. There were 3 deaths under 1,000 grams, only 1 other premature death; 3 due to congenital anomalies; 1 cerebral hemorrhage; 1 pneumonia; 3 hydrops due to erythroblastosis. In the second half of this year we feel that only two deaths could have been prevented by the pediatrician; one was the premature breech, second twin, who was inadequately suctioned at birth and at autopsy was found to have total atelectasis. The other was the pneumonia case due to Friedlander's bacillus which might have been saved by chloromycetin, but this is questionable as the mother also had Friedlander's in the throat culture, and the membranes were ruptured while the patient was in hard labor for 36 hours, and the infant expired within 48 hours.

If the reader will compare the figures of the two halves of this year (1954), he will note the great salvage in the premature group for only one of over 30 prematures, who weighed over two pounds, in the second half of the year was lost.

The rules for prematures are as follows: Suction the stomach and pharynx with a DeLee catheter at delivery, and repeat on arrival in the nursery. Give no positive pressure, except by a trained anesthetist, or in short quick breaths which cannot possibly rupture alveoli. After establishing an air way, give oxygen in the delivery room until color is healthy, then, transfer to the nursery as soon as possible. Be sparing of stimulants. If morphine was given to the mother, give the specific antidote, which is Nalline or N-allylmorphine. If caffeine or coramine is required, give in minute doses as they increase the need for oxygen when oxygen is not being taken well by the baby. Keep baby warm, do not handle roughly nor spank. Use gentle artificial respiration with the legs on abdomen if necessary. Transfer to a separate nursery as soon as possible under the constant vigilance of the head nurse. Give oxygen with alevaire for at least 48 hours. Do not use airlock if the baby is breathing at all and maintains its color well in oxygen with alevaire. Give vitamin K, 5 mgm., every 8 hours, times three. Give penicillin if positive pressure was used or any chance of contamination was present. Delay eye treatment if child is critical. Give nothing by mouth for at least 24 to 48 hours, then only plain water or glucose water. Keep temperature and humidity at 85° F., not too warm. Discontinue oxygen as soon as possible to prevent retrolental fibroplasia. Give formula, 0-lac 1 to 2, 60 calories or 60 cc. per pound per 24 hours. Feed by gavage if weak or under 2 pounds every 3 hours.

In reviewing the still birth records, it was found that not all the perinatal mortality rate is attributed to pediatricians, for some deaths could have been prevented in the obstetrical field. The obstetricians believe that they should be allowed a higher rate of cesarean sections; an increase to at least 6 per cent or higher if necessary to save the lives of babies. Cesarean section should be considered for those in hard labor over 24 hours, and for those whose second stage lasts more than two hours, if they cannot be delivered otherwise. If there is slowing of the fetal heart, there may be prolapsed cord, and the baby's life may be saved by cesarean

section. A diabetic mother may often have a live baby if delivered by cesarean section at the thirty-fifth week of pregnancy. Hypertension is sometimes an indication for cesarean section to prevent abruptio placentæ, and l ss of the baby. Of course, inadequate pelvis, placenta prævia, abruptio placentæ are indications for cesarean sections.

In obstetrics, an antibiotic given to the mother, if the membranes are ruptured more than 24 hours, may prevent pneumonia in the baby and septicemia in the mother. In obstetrics, vitamin K may be given to the mother if the baby is premature. It might be advisable for the obstetrician to have a pediatrician present in a known premature, or erythroblastotic infant; during all cesarean section cases, and in any deliveries in which difficulty with the baby is anticipated.

In preventive obstetrics, it is as important for an underweight mother to gain as it is for an overweight mother to reduce. Too strict a diet in early pregnancy has been found to cause premature delivery, for prematurity is twice as prevalent in underweight as in overweight or normal mothers. Although it is somewhat controversial whether or not to give stilbestrol to habitual aborters and diabetics, we feel it cannot harm, and may save some babies.

In conclusion, the neonatal death rate at Hillcrest Memorial Hospital has been materially reduced in 1954. We believe it can be reduced even more in 1955 if constant vigilance is practiced, and the knowledge already gained is utilized, while we seek to further our knowledge each year.

PEDIATRICS AT THE TURN OF THE CENTURY

From time to time the Archives, which was the first Children's Journal in the English language, will reprint contributions by the pioneers of the specialty over fifty years ago. It is believed that our readers will be interested in reviewing such early pediatric thought.

DIABETES IN INFANTS AND YOUNG CHILDREN*

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It is not the object of this paper to attempt to throw new light on the general aspects of diabetes, nor to try to show any difference in the etiology, symptoms or pathology of the disease as it occurs in the young, from the condition as found in adults. I wish to emphasize, from the data relating to the occurrence of diabetes in infants and young children, its frequency, and almost invariably fatal outcome.

Because of our belief in its rarity, or our liability to omit that important part of every physical examination, the complete urinalysis, each of us may have had under our care unsuspected cases of this disease.

I shall discuss the possible importance of sugar abuse in the production of the condition, and bring to your notice the experience of others demonstrating the peculiarly short course of the malady. Whatever reference I may make to the *general* etiology, symptoms, and pathology have place in this paper only in so far as they lend completeness.

Diagnosis: Difficulty and Importance. Diabetes in infants is also of extreme interest in point of diagnosis, for, although the figures for all ages give relatively very few cases below fifteen years of age, statistics gathered from the records of disease in *childhood* furnish us so many cases that we are led to the conclusion that diabetes in the young frequently escapes detection by the practitioner whose chief interest is in adults. The difficulty experienced in obtaining urine specimens from young children is perhaps partly accountable for this.

In discussing the practical points in connection with the diagnosis

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of diabetes in children, we must always consider the relation of diabetes to surgical conditions, its influence on the occurrence of traumatic lesions, and its effect on the course and prognosis of such surgical interference as these injuries may necessitate. Attention is frequently called to cases of glycosuria following head injuries. Redard has demonstrated this urinary condition in his general surgical experience. Although these patients showed transient glycosuria without any other diabetic symptoms, nevertheless they add their warning against operations upon cases of possible diabetic tendency. Krausch has found that the carbohydrate capacity is much diminished at the time of any injury and returns to normal only after several days have elapsed. This suggests the possibility of converting a mild or transient form of the disease into a more severe type by the shock of operation and anesthesia. Among diabetics, rapid spread of infections, due to the lessened resistance, is the rule, and therefore such operations as those for the removal of adenoids and tonsils should be undertaken on diabetics only when the need is urgent.

While arteriosclerosis and vasomotor disturbances do not play an important part in the cases occurring among children, still the acid intoxication and liability to coma following operative shock are very great in the young and modify much the surgical convalescence.

Definition. In the light of our present knowledge we have to consider diabetes as a disease characterized by a deficient power of oxidation of both carbohydrates and fats, resulting in an increased percentage of glucose in the blood, and an excretion of sugar in the urine; and that the amount of sugar so excreted is an index of the reduced oxidation of carbohydrates; that the presence of, and amount of oxybutyric and diacetic acids and acetone in the urine express roughly the degree of diminution of fat oxidation, and that the condition is due either to the reduction or lack of a ferment normally produced in the pancreas, liver and muscles, or simply to some unexplained metabolic defect.

Literature: Frequency. The pioneer in the investigation of diabetes in children was Külz, who in 1878 collected 111 cases. At about the same time Reden wrote of 32 cases, followed by Stern with 117, and by Saundby with 159. In 1895, Wegeli published a very comprehensive article, including the above-mentioned

papers and adding thereto 108 cases which he found in the literature up to the time of his own writing. This gives us a total of 527 cases collected by these five men during a period of seventeen years, 57 cases having appeared in more than one of the reports above-mentioned.

Statistics vary widely as to the relative frequency of diabetes in the young. Thus, Pavy reported 1,365 cases of all ages, among which were only 8 under ten years. Prout collected 700 cases, of which 1 was under ten years. On the other hand, of Reden's 1,003 cases, 50 were below ten years, 47 between ten and fifteen years; and in Saundby's 2,011 cases, fifteen occurred in children below five years, 58 below ten years, 78 below fifteen years.

Although in New York City during the ten years from 1889 to 1899, only 14 deaths from diabetes were reported in children under four years of age, at about the same time Hagenback had no trouble in collecting a series of 77 cases, all of them under one year.

To sum up, Pavy, Prout and Meyer, taking diabetes as it came at all ages, found together only 11 cases in children, or less than one-half of 1 per cent of a total of 2,240 cases examined. Reden and Saundby, working for records of the disease in childhood, reported, out of 3,014 cases, 394 cases, or over 13 per cent occurring in children under fifteen years of age. The former figures support the general belief in the rarity of diabetes in youth. The latter argue strongly for the suspicion that many such remain undiagnosed.

Age. An analysis of Wegeli's cases shows 29 occurring in the first eight years, 81 during the years from five to ten, and 42 between the ages of ten and sixteen years. We may state, then, with some reason, that the incidence of diabetes in infancy is greater than is commonly believed.

Sex. In a comparison of sex, Pavy, Külz and Stern make the number greater in females than in males. Wegeli and Saundby believe the occurrence to be the same in both sexes. A review of all available figures indicates the disease to be more frequent in females in infancy than in adult life.

Etiology. The importance of inheritance in the etiology of the disease is emphasized by Wegeli, Külz and Stern. In one series of 28 cases, 7 had a diabetic family history. In the cases in which I have found complete histories on this point, out of

8, 4 had diabetes in the family, and among these there figured one sister, an uncle, a cousin and three grandparents—in 1 case both being affected—with no signs of diabetes in the patient's own parents.

I have among my notes the following case which is significant in relation to this point of heredity. The paternal grandmother died of diabetes at fifty-four years, the grandfather of tuberculosis. Parents are living and well. The first child, normal and healthy up to the fifth year, died at six and one-half years of diabetes. Her illness dated from a severe attack of measles eighteen months before. The second child, now eight years old, is normal. The third child at four years developed diabetes, which was active for one year and has been latent for the past twelve months. The last child, normal and healthy up to four months ago, sustained at that time a severe and continued fright and nervous shock, and has since shown the symptoms of a mild diabetes.

That there exists, in all these cases of infantile diabetes, a condition at birth predisposing to a breakdown in the glycogenic function is probable; it is doubtful, however, that the disease is, strictly speaking, congenital, our only definite pathological evidence being that the changes noted in the pancreas are as often of the nature of a compensatory hypertrophy as of a structural or secretory deficiency originating in utero.

We find among the more important causes mentioned in connection with the diabetes of childhood a neurotic inheritance, trauma and acute infectious disease. I have seen no reference to the influence of race which is often noted among adults. Other factors so frequently associated with the onset of the condition, namely, chills, bad hygiene, rapid growth and dentition, can certainly exert only a secondary etiological influence. A case of lumbar Pott's disease is reported with all the symptoms of diabetes which cleared up completely on the reduction of the kyphosis. This is worthy of mention only as it cites a lesion related to the cerebrospinal tract, producing symptoms of true diabetes and not, as is more frequently seen, those of mere glycosuria.

Glucose Capacity in Children. There is little to be found in literature bearing on the relation between the amount of sweets taken by children and the production of diabetes among them through overstrain of the glycogenic function.

Although the glucose capacity of adults, that is, the greatest amount which can be ingested at one time without the excretion of this sugar in the urine, has been well established at 100 to 150 grams, and is now being used as a test of the hepatic function by clinicians and many insurance companies, there is no data as to this capacity in infants.

In order to learn something of this, I have for some time been feeding to children varying amounts of glucose and examining the urine next passed. Two hours after eating, the bladder was emptied and the glucose given. Examination for sugar in the urine next voided, Fehling's solution being used, showed that children between three and five years had positive urinary findings after ingesting 30 grams; between five and ten years after 50 grams.

Before beginning this series of tests, I was of the opinion that the infant capacity was relatively low, and at first found many children who had postitive Fehling reactions after taking from 15 to 25 grams of glucose. The averages of the total number of urinalyses showed so much greater ability to store the glucose that we were forced to the conclusion that children were quite as able to handle their sugars as adults.

The glucose capacity, then, for the first ten years, may be put at from 30 to 60 grams. As capacity is perhaps more directly commensurate with bulk than with age, it is interesting to note that a comparison of the average bulk for this age, i.e., 36 pounds, taking the mean of the weights from one to ten years, and the average adult weight of 150 pounds, indicates a slight advantage in favor of the child's capacity.

Of equal importance in this comparison of infants and adults, is the fact that sugar or starches make up more (about one-half) of the diet for the first ten years, and less (about one-third) of the adult food. There is good ground for the argument that the child is better equipped for sugar digestion than the adult. In favor of this view stands the theory that the parenchyma of any body viscus, the liver for instance, is proportionate to its volume, and that in growth we have a hyperplasia of pre-existing cells rather than a production of new cellular elements.

Vierordt proves that the child is better provided with liver substance than the adult by his figures placing the liver as equal

to 4.4 per cent of the body weight at four years, and only 2.7 per cent of the adult body weight.

Of more value, however, than experiments and theories which we have cited to show that the child can withstand relatively a little more sugar at one dose than the adult, that he has to do considerably more starch digesting to supply his body needs, and that for this he is equipped at birth with all the active liver cells that he is ever going to have and a bigger percentage of liver substance, is the practical experience of each one of us that overstrain of any sort is more easily produced in early life when none of the bodily functions have the resistance to external diversion from the normal which exists at maturity. Bearing both in mind, it seems reasonable to correlate the well-known abuse by many children of all forms of sugar with the appearance of diabetes among them.

From 8 cases occurring in the practice of Dr. Holt, I have been able to obtain these facts, which are so significant as to lead us to believe that careful investigation of a number of cases would tend to show that this matter of the amount of sweet ingested has at least some part to play in the production of infant diabetes. Of these children, five were known to have been taking large amounts of sugar over varying periods of time. One, a girl of five years, had been taking for eighteen months liberal quantities of honey and jam every night, and for some time before the onset had eaten of these more freely than usual. The family history in this instance was negative. One, a girl of seven years, had free access to the candy box, it being not an unusual thing for her to eat a pound in two days; and another case had a record for some years of ½ ounce of sugar a day in addition to the sugar of her regular diet. Two others were said to have had a good deal, this probably meaning several times the amount that would be allowed by a careful nurse. The remaining three patients furnished no data on this point, but taken with the frequently reduced sugar capacity in children, even this meager evidence indicates that the relation of such excretory strain to the appearance of diabetes may be, in some cases at least, a very close one.

Symptoms. The symptoms in youth offer us no peculiarities. Attention was drawn to the condition in a great majority of the patients by an increased thirst, usually accompanied by some

change in disposition, beginning with fretfulness and disinclination to play or move about. Increase of appetite is likely to be marked only after the successful institution of a proper regime. Emaciation is, of course, marked in those patients that do badly from the start, but in others there may be no loss of weight, and in two that I have been able to observe there was some gain up to the advent of the intercurrent disease which terminated them fatally. The prominent early symptoms in the individual cases that I have collected have been: twice, thirst, pain, and tenderness over the region of the pancreas; once, a general edema and urticaria. The loss of knee-jerks I found mentioned in only 1 case. The reflexes are often lost or diminished, with the increase and decrease of the sugar in the urine.

In connection with my work at the Manhattan Eye and Ear Hospital, I have been frequently led to a suspicion of this condition in adults by the failure of an apparenty healthy wound to heal. So in childhood, one should look carefully for evidences of diabetes in those cases which under the best conditions persist as victims of malassimilation.

The Urine. The urine varies in amount between 700 and 7,000 cc. in twenty-four hours, with a specific gravity of 1.020 to 1.040, the extremes in Wegeli's series being 1.008 and 1.070. These low specific gravities are interesting in connection with Hart's report of 50 cases of diabetes mellitus, chiefly in adults, in which the readings were between 1.006 and 1.018. The maximum amount of sugar in twenty-four hours was 1,240 grams, the average being about 4 per cent, and ranging between 6 per cent and a fraction of 1 per cent. This sugar content fluctuated with the time of day, and with the ingestion of food, being lowest at night, highest about mid-day and again in the early evening.

The presence of albumin was variable. In Wegeli's cases it appeared in thirteen, and in almost all the fatal cases it was found before death, furnishing ground for his belief that its appearance is an indication of a rapidly fatal termination of the disease.

Without at that time recognizing their significance, Epstein first noticed the short, thick, hyalin or finely granulated casts which, later, Külz, Aldehoff and Wegeli came to consider as the certain forecast of approaching coma. In 20 patients these were found just before, or during, coma in urines that had previously

been free of formed elements. The presence of acetone and diacetic acid in the urine was considered as a very grave sign and was mentioned in almost all of the recorded cases. Both of these bodies are, however, much more likely to appear in infantile than in adult urine. In grave cases oxybutyric acid may be present in large amounts. To neutralize this excessive acidity, the ammonia content of the urine is uniformly increased. Herter mentions a case in which a large per cent of the total nitrogen was excreted in this form.

Acetone and diacetic acid, products of fat and to a less degree of proteid metabolism, have been found at times present in greater quantity than could be furnished by the food ingested, this suggesting that their presence is not entirely due to lack of carbohyrate and fat oxidation, but also to the breaking down of the body proteids. Their abundance is an index of the probability of coma, as they are increased in this condition many times, and easily reduced by the addition of more carbohydrate to the diet.

The Blood. The blood in diabetes shows few and inconstant variations from the normal. There is usually an increase in the sugar normally present. Anemia is generally not marked in the early stages or in the cases of moderate severity. Bremer's test, depending upon the staining properties of the previously heated smears, and Williamson's decolorization test are irregularly present and are of small diagnostic value. Several investigators, among them Körnchen and Coats, have written on the frequency with which the blood at post-mortem examination is found to be loaded with fat in fine emulsion. Change in the number of leukocytes or variations in the differential count are not common.

Recently, some investigations have been carried on to determine the opsonic index in diabetes. A low index for the staphylococcus pyogenes aureus is so far the only finding, and simply emphasizes the already known low resistance existing in this disease. Hitherto, no relation has been found between the opsonins and the presence or absence of sugar or of the acids in the urine.

Although in many cases the heart is found to be normal, it is reasonable to expect the circulation to suffer considerably from the toxemia existing in diabetes. Estimates of blood pressure in adults suffering from diabetes seem to prove that the disease per se has no tendency to affect the pressure, but that the occurrence of

the complications incident to it individually explain the hyper- or hypo-tension occasionally noted.

Duration. The course of the disease is much shorter and more rapidly fatal in children than in adults. In general, the younger the child, the shorter the duration of the illness. Bogoras has in his records:

14	cases	with	a	duration	of one month
19	"	"	"	"	" six months
3	"	"	"	"	" one year
1	case	"	"	"	" two years
1	"	of longer duration			

He does not give the ages of these patients.

In Tyson's entire experience he has seen only 1 case, that of a girl of twelve years who made a permanent recovery.

Of Wegeli's 108 cases, 69 died while under observation; 6 recovered, and during the time for which they were followed showed no symptoms of relapse; 9 patients showed improvement and clearing up of all symptoms, but were not observed beyond three months, and their final outcome was unknown.

The diabetic condition is often interrupted by a latent period during which there is a suspension of all active symptoms, the patient appearing to be in perfect health or suffering only from a mild nutritional disturbance. A case that I was able to follow from onset to termination illustrates this phase. The patient was a girl in good circumstances, whose family history was negative and birth normal, and who was considered a strong, healthy child up to the age of four and one-third years. It was then noticed that she was drinking a good deal of water both by day and by night, and was becoming unusually irritable and easily tired. An attack of rötheln, followed by rapid emaciation, asthenia and further irritability, led to an examination which revealed 120 to 180 grams of sugar to the liter, a trace of albumin, abundant acetone, diacetic and oxybutyric acids, and a few casts. The urine reached the large amount of two to three liters daily. These conditions, with a diminution in the amount of sugar, lasted for two months without other material change, when all diabetic symptoms cleared up and for six months there was steady, though small, gain in weight, the child appeared as well as at any time previously, and urine examinations were repeatedly negative. At the end of this

latent period, the child being then five years old, sugar, acetone and diacetic acid, with a trace of albumin, reappeared and persisted with slight general symptoms until she was seven and one-quarter years, when, after two years, in which the disease was entirely stationary and evidenced only by the urinary findings, death suddenly occurred after a short illness.

The case illustrates the long latent periods possible in the disease, and bids fair to prove an exception to the usual rapid decline accompanying the appearance of albumin, until at seven and one-quarter years her unexpected death occurred.

Thirteen cases, which I have collected from the recent literature on the subject, show:

1 death four days after onset of symptoms
6 deaths three months " " " "
1 death eight " " " " "
1 " one and one-half years after onset of symptoms
4 deaths two and one-half " " " " "

Complications. Reden, Leroux and Simon name as the most frequent complications tuberculosis, boils, pruritus and gangrene, the latter being relatively less frequent in childhood than in adult life.

The generally lowered physical condition of these patients makes the appearance of any complicating trouble of grave import, but the ever present and most difficult problem is keeping the nutrition up to the highest possible plane, without overtaxing the digestive or excretory functions.

Pathology. Evidence in the pathology of diabetes in general is varied, scanty and unsatisfactory. The findings in children differ in no way from those in adult cases. The majority of lesions found post-mortem are due to changes secondary to nutritional disturbance, the exceptions being tumors of the medulla and vagi, primary liver disease, and calculi in the pancreatic duct.

Kidney lesions are noted by Anderson as a fatty and glycogenic degeneration of the epithelium; by Leroux and Liebens, as a parenchymatous nephritis. Jacquemet, in all his cases, found the kidneys congested and swollen. Prevost and Bunch argue for a swelling of the renal epithelium, but no actual degeneration. Leva, later corroborated by Epstein, found a hemorrhagic nephritis and epithelial degeneration.

Landmeyer described a peculiar degeneration of the epithelium, probably glycogenic, and Tichtnor later noticed the same condition, most frequently in cases that died in coma. In these nearly all the tubules were filled with a broken down epithelium and entirely closed off, showing at the bases of their cells large and small fat drops. Although the glomerular capsule presented the same conditions, there was found no interstitial fatty degeneration.

The pathology of the pancreas has been described by Leroux and Leva as a general atrophy of the gland in some cases, in others of the cellular elements alone. In twenty-six autopsies the former condition obtained in thirteen instances; the pancreas was large and hard in five; large and soft in one; simply congested in one; and normal in six.

These papers were published before attention was called to the islands of Langerhans by Opie and others, and, therefore, these lesions may have been overlooked. Evidence as to this particular lesion in the pancreatic condition in diabetes is, at present, divided between hypertrophy, atrophy and vacuolization of the islands of Langerhans.

Two cases reported in which the pancreas was normal, although there was fatty degeneration in the heart, kidneys and medulla.

Röhrig reports a case which on post-mortem examination showed only an occlusion, by calculus, of the pancreatic duct, which had produced behind the obstruction a cyst filled with pancreatic secretion.

The most common lesions of the central nervous system have been new growths and congestion and thickening of the meninges.

Treatment. In the treatment of diabetes the aim of the physician is:

(1) To maintain the bodily nutrition at its highest level by general regimen and feeding;

(2) To keep the excretion of glucose in the urine as low as possible;

(3) To keep the urine free from acids.

For the proper care of diabetes the following are necessary:

(1) The determination of the type of case with which we are dealing; that is, the inquiry into whether we are to handle simply a carbohydrate incapacity, or also a deficiency in fat oxidation, as shown by acidosis;

(2) The discovery of that particular form of carbohydrate which will be best borne by the patient;

(3) A clear method, preferably graphic, of recording data by which exact information can be had of, and comparison made between, the following points:

(*a*) The patient's weight;

(*b*) The amount of urine passed in twenty-four hours, and its specific gravity;

(*c*) The amount of sugar excretion;

(*d*) The quantity of the acids present in the urine.

Daily Regime. For the maintenance of the bodily nutrition, we have at our disposal general hygiene and care, diet regulation, and the use of drugs that will meet special requirements.

Regularity of regime should be first insured by laying out a definite routine for each hour of the day.

The child should awaken and have the first meal, in bed, at a fixed time. He should remain in bed till mid-morning, and then be allowed to be up and out until the hour for the noon-meal, after which he should be well wrapped and made to rest quietly in the open air for at least two hours. He may then be given mild exercise, walking or driving if in good condition, or massage if passive exercise is better borne. Supper should be not later than 6 P.M. and bed at 7.

The sleeping room should be ventilated as for a tuberculous case. During his waking hours the child is to be interested, but not excited; during the resting time, he is to be left entirely alone. Care is necessary that the clothing be sufficient to keep him warm, but never enough to produce perspiration.

In a word, as much care must be taken to guard against waste of nervous energy and overtaxation of the heat centers from over or under clothing, and to provide proper fresh air at all times, as is used in regulating the diet. The care of such accompanying conditions as rickets and chronic digestive disorders is secondary, not even to treatment of the diabetes itself.

I have dwelt at such length on this phase of the treatment, because we have no cure for the disease itself. Carlsbad has enjoyed its reputation as a place where diabetes may be cured, only because of the benefit derived there from the carefully regulated daily regimen to which patients are subjected. In children we

may look for much better results from this course than we could hope for in the case of an adult.

As to the type of case presented, much is learned from the first examination and urinalysis. The former will reveal perhaps a fairly-nourished and otherwise normal child in the early stages of the disease, without complications, of equable temperament and good training, or a patient already emaciated, spoiled, the victim of previous dietary abuse, rachitic, and with a worn-out, starved nervous system.

The urinalysis at once stamps the patient as one with a small percentage of sugar and no acids, or presents the reverse picture of greatly reduced carbohydrate capacity and power of fat oxidation; but it is for the subsequent analyses to reveal the amenability or obstinacy of the case to treatment.

Diet: Carbohydrate. The discovery of the variety of carbohydrate best suited to the patient should be the first result of the institution of the diet. Semiweekly urinalyses and weights may show increasing carbohydrate tolerance with certain starches, and so indicate which of these is most easily handled.

The starches of oatmeal, potato and milk and such suger as levulose, which is present in fresh fruit and honey, are sometimes found to have no effect in increasing the sugar excreted.

The patient should be put on a standard diet, suited to his age and condition, and as free as possible from carbohydrate. Then a supplementary diet consisting principally of that carbohydrate found to be best borne, together with the other allowable starches and sugars, should be held in reserve, from which is added more or less according to the varying carbohydrate tolerance shown.

Periods of complete, or nearly complete, abstinence from carbohydrate should be alternated with periods allowing a fair amount of starch and sugar, the latter best coming at such time as the sugar is low in the urine.

The most reliable sign that more sugar is needed is the presence of diacetic acid, as shown by the ferric chlorid reaction. When the reaction becomes marked, carbohydrate should be administered freely or coma is apt to appear.

Because of the monotony of the diet, the resources of the physician will be sorely taxed in providing enough legitimate

variety to keep the older children taking their food well. I shall not attempt to go into the food lists, with their varying carbohydrate contents and caloric values, as this information is easily accessible to all.

If, in spite of all effort, the condition of acidosis supervenes, the administration of alkalies is indicated. Soda bicarbonate is to be given; by mouth in the usual case, intravenously in the event of coma. The amount of the drug necessary depends on the amount of the ammonia output in the urine. This averages from .5 to 1.0 gram in twenty-four hours, and may increase to 12 grams. As the quantitative tests for ammonia are rather beyond the reach of the usual office scope, we must depend in practice on the depth and persistency of the diacetic reaction for our warning that alkali is needed.

The ultimate result of this treatment has, however, not been very encouraging, indicating that possibly the acidosis is merely a symptom of some deeper metabolic defect giving rise to the toxemia, and that the coma is not due to the excessive acid alone.

There may be in the near future some additional light on the method of treatment by use of internal secretions through the work that is being done on the hormones, notably that extract of the duodenal mucosa known as secretin; but at present we have no direct method of treating this malady and can get but little help from the use of drugs.

DEPARTMENT OF ABSTRACTS

MARKS, J.; GAIRDNER, D. AND ROSCOE, J. D.: BLOOD FORMATION IN INFANCY. CORD BLOOD. (Archives Disease in Childhood, 30:117, April 1955).

From analysis of cord blood from a large series of infants normal haematological values have been derived. The normal cord blood haemoglobin level ranges from 12 to 22 g. No relationship between cord blood haemoglobin and foetal maturity was found. The haemoglobin level at 7 weeks and 9 weeks of age was determined in two groups of infants: (a) those born with a high normal cord haemoglobin and (b) those born with a low normal cord haemoglobin. At 2 months of age each group had a similar haemoglobin level of about 11g. per 100 ml. AUTHORS' SUMMARY.

HOUGH, J. V. D.: THE MECHANISM OF ASPHYXIA IN BILATERAL CHOANAL ATRESIA: THE TECHNIC OF ITS SURGICAL CORRECTION IN THE NEWBORN. (Southern Medical Journal, 48: 588, June 1955).

Infants are in grave danger of asphyxiation if nasal breathing is obstructed. They do not breathe instinctively through the mouth. This paper presents the mechanisms of respiratory obstruction shown by x-ray films and drawings. Correction of all bilateral posterior choanal atresia should be accomplished early in the newborn. Few cases have been operated early to date. A detailed description of a simple surgical method of treatment has been presented which may be of value to those who encounter this condition in their practice. AUTHOR'S SUMMARY.

JEANS, P. C.; SMITH, M. B. AND STEARNS, G.: INCIDENCE OF PREMATURITY IN RELATION TO MATERNAL NUTRITION. (Journal American Dietetic Association, 31:576, June 1955).

The incidence of prematurity rose sharply with decrease in the nutritional status of 404 pregnant women of low income living in a rural state. The most common nutritional deficiencies observed were calcium and protein. Among the better nourished women, premature delivery tended to be associated with frequency and total number of pregnancies and with multiple birth. Among the least well nourished, the incidence of prematurity

showed less relationship to number or frequency of pregnancies. It was observed that lowest birth weights, low vitality, and larger number of deaths in the newborn period occurred among infants born to the most poorly nourished mothers.

AUTHORS' SUMMARY.

LANGE, R. D. AND HAGEN, P. S.: HEMOGLOBIN C DISEASE IN IDENTICAL TWINS. (American Journal Medical Sciences, 229:655, June 1955).

The case histories and laboratory findings of hemoglobin C disease in identical Negro twins have been presented. The diagnosis may be suspected by the presence of splenomegaly, anemia, reticulocytosis, numerous target cells and absence of sickling, but electrophoretic studies are essential for confirmation. Red cell survival studies showed a markedly shortened survival time of autotransfused cells, including the presence of a hemolytic process. From a clinical point of view, in our subjects hemoglobin C disease was an apparently benign condition. AUTHORS' SUMMARY.

SNYDER, C. H.: PRACTICAL SCHEME FOR FLUID AND ELECTROLYTE THERAPY IN CHILDREN. (Journal American Medical Association, 158:1004, July 23, 1955).

For the conduct of intravenous fluid and electrolyte therapy in medical and surgical patients of the pediatric age group, we employ only 5 different solutions, i.e., 5% glucose, 10% invert sugar, 3 M sodium chloride, 3 M potassium chloride and 1 M sodium lactate. For each patient, once each day, a proper mixture of these solutions is prepared to provide for all his needs for a 24-hour-period. In prescribing these fluids we give the following amounts of fluid: (1) for daily maintenance, per square meter of body surface, 1,500 cc. of water, 30 mEq. of sodium chloride and 20 mEq. of potassium chloride; (2) for replacement of current abnormal losses (diarrhea, vomiting, gastric suction, etc.) per liter of such fluid lost, 1,000 cc. water, 135 mEq. of sodium chloride and 15 mEq. of potassium chloride; (3) for correction of dehydration, assuming 10% weight loss through dehydration, per Kgm. body weight, 80 cc. of water, 6 mEq. of sodium chloride and 4 mEq. of potassium chloride (for moderate dehydration, only half these quantities); (4) for beginning therapy of dehydrated patients, a

potassium free "initial mix" containing, per liter, 50 mEq. of sodium chloride and 25 mEq. of sodium lactate. Potassium is given only after renal function has been established. Certain precautions must be observed in the application of these rules, particularly in regard to the dangers of potassium therapy. AUTHOR'S SUMMARY.

BETTAG, O. L.; PLOTKE, F. AND STERLING, H. M.: EFFECT OF GAMMA GLOBULIN ON MEASLES. (Public Health Reports, 70:353, April 1955).

An epidemic of measles followed by an epidemic of German measles occurred in a residence school for 92 orthopedically handicapped children, 16 having no previous history of exanthemata. The possibility of pregression of basic conditions or of seriousness of sequelae prompted an attempt to prevent the disease in 10 pupils by the administration of 0.1cc. GG/lb. body wt. I.M. on the 4th day after exposure; 24 others received 0.02 lb. body wt. to modify the illness; 58 students, who had positive histories of measles, received no GG and, therefore, were not quarantined. Six children developed measles at least 11 days after receiving a "preventive" dose of GG. Of these, 4 had mild and 2 had moderate measles, but none had complications from this disease. One child suffered rapid progression of the basic condition following a subsequent attack of German measles. A previous history of measles was of no value in deciding who should receive GG, since 20 students with such histories developed measles, 4 German measles, and 3 both. Three had complications of some type. GG in the dosage currently recommended for prevention of measles failed to protect 6 out of 10 children to whom it was administered. GG in "modifying" dosage apparently failed to modify the disease in 4 out of 19 students to whom this dosage was administered. There was no evidence that GG prevented or modified German measles.

AUTHORS' SUMMARY.

MEYER, M.; MIDDLEBROOK, G. AND ROBINSON, A.: THE TREATMENT OF PRIMARY TUBERCULOSIS IN INFANCY. (Journal Pediatrics, 46:398, April 1955).

(1) The management of the infant under one year with primary pulmonary tuberculosis has received inadequate attention in the past. (2) The malignant forms of progressive primary tuberculosis,

i.e., miliary tuberculosis and tuberculous meningitis, occur with greatest frequency during infancy, and should be prevented whenever possible. (3) All infants and children should routinely be tested with tuberculin in order to detect early the presence of primary tuberculosis. (4) BCG should be given to those likely to be exposed to tuberculosis. (5) Infants with a positive tuberculin and negative x-ray findings should receive a course of INH. (6) Infants with a positive tuberculin and positive x-ray findings should receive INH and streptomycin sulphate. AUTHORS' SUMMARY.

SCHEELE, L. A. AND SHANNON, J. A.: PUBLIC HEALTH IMPLICATIONS IN A PROGRAM OF VACCINATION AGAINST POLIOMYELITIS. (Journal American Medical Association, 158:1249, Aug. 6, 1955).

It is erroneous to assume that absolute safety can be assured, but it is believed that recently amended requirements for manufacture and safety testing of poliomyelitis vaccine assure the production of potent material that is safe, as tested by present tests for active virus detection, and that the risk of such vaccine transmitting poliomyelitis is negligible. Vaccine produced by 4 licensed manufacturers has been used in approximately 5 million children in 1955 with no untoward results. A total of 114 cases of poliomyelitis have been reported in vaccinated individuals through May 31, 1955. Of these, 79 were associated with the product of one manufacturer, which had been used in a total of approximately 409,000 persons. The widespread use of the poliomyelitis vaccine can be expected to prevent a high percentage of paralytic poliomyelitis cases, especially in children 6 to 9 years of age, and probably in other age groups as well, when supplies become available. It is believed that children younger than 6 years, children older than 9, and adults should receive the vaccine and that studies should be made to ascertain its preventive value against paralytic poliomyelitis in these age groups. Additional experience with the vaccine in the hands of private practioners and public health officers will lead to further improvements in the control of poliomyelitis. Final decisions on the use of the vaccine remain the responsibilities of individual physicians and health officers. AUTHORS' SUMMARY.

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